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Prenatal Stress, Maternal Immune Dysregulation, and Their Association With Autism Spectrum Disorders

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Abstract

Purpose of Review—While genetic factors are a major etiological contributor to autism spectrum disorder (ASD), evidence also supports a role for environmental factors. Herein, we will discuss two such factors that have been associated with a significant proportion of ASD risk: prenatal stress exposure and maternal immune dysregulation, and how sex and gender relate to these factors.

Recent Findings—Recent evidence suggests that maternal stress susceptibility interacts with prenatal stress exposure to affect offspring neurodevelopment. Additionally, understanding of the impact of maternal immune dysfunction on ASD has recently been advanced by recognition of specific fetal brain proteins targeted by maternal autoantibodies, and identification of unique mid-gestational maternal immune profiles. Animal models have been developed to explore pathophysiology targeting both of these factors, with limited sex-specific effects observed.

Summary—While prenatal stress and maternal immune dysregulation are associated with ASD, most cases of these prenatal exposures do not result in ASD, suggesting interaction with multiple

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Compliance with Ethical Standards

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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other risks. We are beginning to understand the behavioral, pharmacopathological, and epigenetic effects related to these interactions, as well as potential mitigating factors. Sex differences of these risks have been understudied but are crucial for understanding the higher prevalence of ASD in boys. Continued growth in understanding of these mechanisms may ultimately allow for the identification of multiple potential points for prevention or intervention, and for a personalized medicine approach for this subset of environmental-associated ASD cases.

Keywords

Autism spectrum disorder; Immunity; Antibodies; Stress; Prenatal; Gene × environment

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is behaviorally characterized by impaired social communication and the presence of repetitive and stereotyped behaviors [1]. Current estimates suggest an incidence of one in 59 among 8-year-old children from the USA [2]. Understanding mechanisms that underlie ASD is critical for efforts towards prevention or early intervention of the disorder. While the etiology of ASD is not fully understood, genetics is a well-established risk factor [3]. However, the importance of non-genetic risk factors is being increasingly recognized [4], with heritability estimated at 0.83 by the latest, more conservative, analysis [5•]. While progress has been made towards gaining an understanding of genetic factors, including the development of animal models of ASD candidate genes [6–9], environmental risk factors are less understood. Furthermore, as autism is predominantly male, with a ratio of males to females of at least 4:1 [1], it will be critical to understand how any of these risk factors might have sex-specific effects.

The developmental origins of health and disease (DOHaD) hypothesis proposes that the environment experienced during development in utero influences health after birth [10••]. Recent studies demonstrate that adverse environmental exposures affect neurobiological development, including effects salient to ASD. Furthermore, gene × environment interaction (G×E) is a critical component these effects, with offspring sex contributing not only sex chromosomal but other gene differences as well. Therefore, understanding the mechanisms of environmental risk may allow for possible prevention, at least in a subset of ASD cases with known genetic risk factors, where the biological effects of environmental exposure can be enhanced (Fig. 1).

A number of environmental factors have been recognized to be associated with increased incidence of ASD. For example, data are mounting regarding maternal exposure to pollutants resulting in increased risk of ASD. In particular, there is a growing body of literature implicating air pollutants [11•, 12–14], with evidence of an interaction with polymorphisms of the tyrosine kinase MET receptor gene [11•]. There may also be a modestly increased risk of ASD with exposure to medication use in pregnancy, most significantly valproic acid [15]. Earlier research suggested that the risk of ASD in association with exposure to β2-adrenergic agonists, commonly used to arrest premature labor, is affected by maternal polymorphisms in the β2-adrenergic receptor [16]. Other

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factors are also being explored and identified including pesticides, endocrine disrupting chemicals, and maternal dietary factors, including a lack of folate supplementation during early pregnancy [17•, 18•, 19]. Increased parental age and short intervals between pregnancies have also been observed as risk factors [20, 21]. Other factors have been revealed to have no association with ASD, such as heavy metals [22].

Among environmental factors, maternal stress exposure during gestation may be an important factor in autism [23–25]. Maternal immune dysfunction has additionally been one of the most robust, non-genetic factors associated with ASD [26, 27••]. Herein, we will discuss recent advances in understanding the relationship between these factors and ASD, and the sex-specificity of these effects.

Prenatal Stress

Recent evidence has suggested that among environmental factors, maternal stress exposure may be an important factor in autism [23–25]. Psychological stress during pregnancy is important more broadly in behavioral and developmental outcomes in humans [28]. Early personality development in children, schizophrenia risk, and emotional disturbances are all impacted by maternal stress, among other effects [29–32]. Relationships between maternal stress and a range of adverse behavioral outcomes in offspring are also reported in animal models, including abnormal behavioral fear and anxiety-like responses and abnormal physiological stress reactivity in offspring that persist into adulthood [33, 34].

The extent of this risk for ASD has been explored across multiple different methods (Table 1). Initially, findings were discovered from surveys completed by mothers of children with autism, Down syndrome, and neurotypical controls regarding the history and timing of prenatal psychosocial stressors corresponding to major life events on the Social Readjustment Rating Scale. A higher overall incidence of stressors was found among mothers of children with ASD compared to other groups. Specifically, a peak in reported stressors was observed among mothers of children with ASD at 25–28 weeks gestation, but was not observed in the other groups [24]. Similar results have been observed by another independent group, showing a relationship between the occurrence and severity of tropical storms in Louisiana during the 5th–6th month of gestation and with the incidence of autism births [25]. Larger epidemiological studies largely support this relationship between prenatal stress and autism. One Danish national registry study suggested against an association between maternal bereavement and ASD [35], but an association was observed before accounting for covariates such as maternal psychiatric conditions [35]. Another Danish national registry study found that maternal psychiatric conditions were one of the strongest prenatal risk factors for ASD [36]. A Swedish registry study also confirmed a relationship between 3rd trimester stress exposure and risk of ASD [37••]. Furthermore, results from another large dataset, the Nurses' Health Study, showed that maternal exposure to partner abuse during pregnancy is strongly associated with ASD, although the timing of exposure with the strongest association was found to occur earlier in the gestational timeframe [38••]. While some of these studies did not explore whether there was a preferential association with stress in males, there was a trend that did not reach significance towards stronger association of prenatal stress with autism in males in the Louisiana tropical storm study [25],

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and the Swedish registry study did not find a significant sex interaction [37••]. Children in utero in New York City during the September 11th terrorist attacks were found to be 7–9% more likely to be in special education classes [39], although no specific data was available regarding autism diagnoses. Prenatal maternal stress was also recently found to predict ASD traits in offspring after a major Quebec ice storm, but there was no interaction with the sex of the child [40•]. Finally, a recent study reported that children with ASD that had been exposed to prenatal stress represent a more severe group than those with no history of prenatal stress exposure [41••].

Stress Susceptibility

In all of these studies, a significant proportion of stress-exposed mothers had unaffected children. To explain why prenatal stressors might contribute to autism only in some cases, a G×E model is of interest. In G×E models, the effect of stress exposure is more salient in a subset of the population. Of particular interest is the serotonin transporter (SERT) gene, which is well studied for its role in stress reactivity. The SERT gene encodes for the SERT protein, which transports extracellular serotonin back into the neuron [42]. Genetic variations in this gene can alter aspects of its function [43–45]. The most widely studied variation is an insertion or deletion of a 44 base-pair segment of DNAwithin the promoter region of the SERT gene, *SLC6A4*, resulting in a long (L), rather than a short (S) allele [42–44]. Presence of the S-allele (SS or LS genotype) has been found to increase the risk of depression after exposure to stress in adult life [46]. Although one later study did not find this relationship [47], a larger meta-analysis has confirmed this result [48]. Presence of the S-allele has also been related to suicidality [49], and susceptibility to anxiety [44], as well as greater activation of the amygdala, the brain region critical for fear reactions [50].

Linkage studies have also associated rigid-compulsive behaviors in autism patients with the region of the genome containing SERT [51]. A variation in a single nucleotide on the gene, Gly56Ala, is additionally linked to increased risk of autism [45], and an additional variant, the Ile425Leu variant, displayed a segregation pattern suggestive of male-biased linkage [52•]. Finally, the S-allele of the SERT gene has been linked to autism in some but not all studies [53–56]. This raises the possibility that the variability in the findings for the S-allele in risk for ASD could be explained in part by the presence of an interaction of this specific genetic variant with stress response, one of the functions most critically regulated by this gene. In this model, risk from the gene requires the additional presence of stress exposure.

To explore relationships between prenatal maternal stress exposure and SERT on offspring social behavior in an experimental setting, we examined mice lacking one copy of the SERT gene (with similar serotonergic effects as the human SERT variations) [57] and control mice exposed to either no stress or a chronic variable stress paradigm, sufficient to induce a corticosterone stress reaction without altering feeding or body weight [58], in the last half of gestation. Offspring of the dams lacking a SERT gene and exposed to prenatal stress had decreased social interaction as assessed by social approach and social novelty seeking with the 3-chamber social approach test [59–62]. The interaction for both social approach and social novelty seeking with offspring sex did not reach significance, but a trend was found for both interactions with prenatally stressed female offspring displaying the lowest degree

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of social interaction [59]. This highlights the role of maternal genetic variants, rather than variants in offspring themselves, interacting with stress to effect neurobehavioral risk, and raises the question of sex-specific effects.

The potential clinical salience of this model has been explored more recently, finding that the relationship between prenatal stress exposure and ASD appears to be mediated by maternal genetic susceptibility to stress as indicated by maternal presence of the S-allele [63••]. Stress surveys similar to those described in the previous study [24] were performed in two independent sample populations. Mothers were examined for both the presence vs absence of the S-allele as a genetic marker and for the presence vs absence of prenatal stress on stress surveys [63••]. If the S-allele is a maternal risk factor for development of autism in children who had exposure to prenatal stress, mothers of children with autism would be expected to more frequently have a history of prenatal stress exposure during pregnancy in the presence of the S-allele. In both samples, the presence of the S-allele and the history of prenatal stress were found to significantly co-segregate in mothers of children with autism within the later critical period of pregnancy suggested in previous work [24, 25, 37••]. Furthermore, there was no increased report of prenatal stress exposure regardless of genotype from these same mothers when queried about pregnancies of unaffected siblings, suggesting that the risk of the S-allele is not an overall increase in recall of stress during pregnancy. This provides support that the S-allele serves as a risk factor gene for increased maternal stress response in development of ASD, and the effect is specific to exactly the same timeframe as reported by previous research [24, 25, 63••].

While the observation of a specific G×E interaction are rewarding, there is a wide variety of genes that can impact or be affected by the stress response. Understanding the mechanism by which the physiological effects of stress might act on the developing brain is necessary to move towards potential intervention efforts, regardless of which stress-associated gene or other factors may be contributing to an increased risk of ASD with prenatal stress, including a range of other variations that affect SERT function [64•]. G×E interactions for prenatal stress exposure has received significant recent interest for neuropsychiatric conditions in general [65••]. Examining these broader pathways of effect on downstream neurobiological systems is of relevance to understanding ASD mechanisms. One such system downstream of stress pathways is GABAergic inhibitory neuronal circuitry. Significant abnormalities in the GABAergic system are found in ASD [66•, 67•], including reduced expression of the GABA-producing enzyme GAD67 in post-mortem brains [68, 69]. Magnetic resonance spectroscopy has shown reduced concentrations of GABA in auditory and motor brain regions and in the frontal cortex in vivo in patients with ASD [70–72]. Prenatal stress has additionally been shown to alter GABAergic neuronal migration and later GABAergic development [67, 73•, 74]. Furthermore, recent evidence suggests that prenatal stress effects on other GABAergic progenitor processes are most prominent in male offspring [75]. Therefore, the effects of prenatal stress on the GABAergic system in ASD are of interest. Furthermore, recent evidence has revealed that prenatal stress-exposed mice from dams with heterozygous KO of SERT have significantly increased striatal dopamine [76•]. It will be of interest to see whether ASD patients exposed to prenatal stress also represent a subgroup with significant dopaminergic changes. Finally, administration of 1% DHA omega-3 fatty acid throughout pregnancy in dams, continuing the diet in pups, reversed repetitive

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grooming behaviors, social interaction abnormalities, and altered striatal dopamine in mice exposed to prenatal stress born from dams with only one copy of the SERT gene as compared to offspring that were untreated with DHA or only given DHA after birth [76•]. The clinical implications of this remain to be explored.

Epigenetic Factors

Epigenetic processes such as MicroRNAs (miRNAs) (small RNA molecules that do not code for proteins but rather participate in regulation of activity of genes in other ways) are among gene regulatory mechanisms that are influenced by environmental factors such as stress. Identifying their potential alteration after prenatal stress will contribute to narrowing the existing gap in our understanding of the mechanism of G×E in autism. Recent research revealed a number of epigenetic changes affecting genes critical to neurodevelopment and the immune system that are associated with stress exposure. With maternal stress exposure in rodents, the placenta showed increased expression in peroxisome proliferator-activated receptors α (PPARα), insulin-like growth factor-binding protein 1 (IGFBP-1), GLUT4, HIF3α, and O-GlcNAc transferase (OGT) specifically for male offspring [77••, 78], of particular interest given the high percentage of males with ASD. Relevant to epigenetic mechanisms, changes in miRNAs were found in offspring brains after prenatal stress exposure when OGT expression was manipulated in placenta.

The heterozygous SERT knockout /prenatal stress exposure model in mice revealed that gene expression and miRNA changes induced by prenatal stress in offspring brains were greatly attenuated by maternal heterozygous SERT knockout genotype, and was associated with genome hypermethylation [79••] (increased methyl groups bound to specific sites on the gene that affect the expression of that portion of DNA). miRNAs also play a significant regulatory role in serotonergic pathways [80, 81] and immune regulation [82], and are affected by prenatal stress more broadly [83, 84, 85••]. Dysregulation of miR-103, miR-145, miR-219, miR-323, and miR-98 in offspring brain was found to result from maternal stress in rats [86••]. Furthermore, inflammatory responses in brain may be altered by miR-323 and miR-98 [86••]. Other miRNAs may be relevant substrates for prenatal stress effects. For example, miR-135 regulates response to chronic stress through interaction with serotonergic activity [87]. miR-155 is critical in immunity and inflammation [82]. Furthermore, the role of specific miRNAs has been reported in regulating serotonergic genes (Let-7a) [81] and SERT (miR-16 & miR-15a) [88, 89] as well as SLC6A4 (miR-325) [90].

Many epigenetic markers are differentially expressed in autism [91, 92], with several involving critical components of the immune system that are detectable in blood [93••]. As blood is a central method by which maternal stress effects are communicated to offspring, it will be important to determine whether prenatal stress-induced expression and methylation changes reported in animals [79••] can be observed in maternal blood in prenatal stress-associated ASD cases. Furthermore, with GABAergic changes observed in ASD [66•], and the effects of prenatal stress on GABA systems and striatal dopamine [73•, 76•], it will be important to see how these epigenetic markers relate to pharmacopathological changes as well as observed behavioral effects. These studies will result in the development of markers utilized to monitor responsiveness in the establishment of novel therapeutic approaches for

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this model. Finally, Bale and colleagues have demonstrated that epigenetic changes with prenatal stress may be transgenerational [94••]. The clinical implication of this transgenerational effect for ASD is as of yet unknown, as are the intriguing findings from animal models demonstrating effects of paternal stress exposure mediated by miRNA [95, 96•].

Prenatal Immune Dysregulation

Under normal conditions, the maternal immune system maintains a pathogen-free and noninflammatory environment for the developing fetus [97, 98]. However, disruption of the normal regulation of immune factors including cytokines, chemokines, and antibodies produced during gestation can have adverse developmental consequences for the fetus. For over 30 years, epidemiological research has found associations between maternal fever and infection (viral, bacterial, and parasitic) around the time of pregnancy and increased risk of neurodevelopmental disorders (NDD), including ASD [99–103, 104•]. The diversity of maternal infections associated with NDD suggests that the maternal immune response may be a critical link between sickness in the mother and altered neurodevelopment in her child.

Cytokine production is a key factor associated with the response to infection. In addition to priming the immune system and controlling immune activation, cytokines also mediate signals between the immune and nervous systems and can help shape neuronal responses and subsequent behaviors, as well as brain growth early in development. Cytokines and chemokines are involved in diverse aspects of typical neurodevelopment, including proliferation and differentiation of neural and glial cells, neuronal migration, dendritic branching, and synapse formation [105, 106]. Some maternal cytokines can cross the placenta during gestation, as in the case of IL-6 [107–109], or act on placental cells to stimulate the downstream production of immune mediators in the fetal compartment [110]. The placenta of males has shown greater susceptibility to cytokines and other changes after prenatal stress [94••]. Fluctuations in the levels of cytokines and chemokines can alter normal neurodevelopmental trajectories, possibly resulting in altered brain morphology and behavior in the offspring.

A limited number of epidemiological studies utilizing midgestational maternal samples have further strengthened the notion that cytokine/chemokine dysregulation contributes towards altered neurodevelopment relevant to ASD in offspring. For example, increased maternal levels of circulating IFNγ, IL-4, and IL-5 at 15 to 19 weeks gestation have previously been reported in 84 mothers of children with ASD relative to 159 mothers of general population (GP) control children [111]. In addition, increased mid-gestational levels of IL-2, IL-4, and IL-6 were found in 49 mothers of children with developmental delay (DD) compared to the mothers of GP controls [111], suggesting that unique cytokine profiles midgestation may influence specific neurodevelopmental processes and result in different NDD. In the Early Markers of Autism Study, archived maternal serum was collected for routine prenatal testing during 15–19 weeks of pregnancy in order to investigate the relationship between mid-gestational maternal cytokines/chemokines and the risk of bearing a child with ASD or DD. In this large, nested case-control prospective study, levels of 22 cytokines and chemokines were measured on an independent sample of 1031 mid-gestational maternal specimens using

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Luminex multiplex technology. A significant elevation in the mid-gestational levels of numerous proinflammatory cytokines and chemokines was found to be distinctly associated with an increased risk of having a child with ASD with intellectual disability (ASD+ID) compared to both the GP and DD groups, with no sex differences reported [112••]. These results suggest that mothers of children with ASD+ID have significantly elevated mid-gestational levels of inflammatory cytokines/chemokines compared to all other groups examined. The immunologic distinction between mothers of children with ASD+ID and those with ASD without ID or DD without ASD suggests that the ID associated with ASD might be etiologically distinct from DD without ASD (Fig. 2). To date, such studies have been largely cross-sectional, with limited assessment of the relative importance of different stages of pregnancy or of differential effects in males and females. Based on studies of gestational cytokine profiles during a typical pregnancy [113, 114], the greatest differences that could be induced in cytokines may occur between the 1st and 2nd trimesters, before the regulation of the maternal immune system strengthens even more in later pregnancy to avoid fetal rejection.

The development of animal models has provided evidence that maternal immune activation or specific immune factor changes can affect behavioral and neuromorphological abnormalities in the offspring [115, 116••, 117••, 118]. These immune-mediated effects have been employed to model several neurodevelopmental disorders, including schizophrenia [119–121], cerebral palsy [122], and ASD [123•, 124••]. Maternal immune activation has been demonstrated to produce long-lasting effects on offspring brain development and behavior [125, 126]. Such studies also provide mechanistic evidence about the role of maternal immune factors in altering neurodevelopmental trajectory.

In addition to cytokine/chemokine dysregulation associated with increased risk of ASD, maternal autoantibodies reactive towards fetal brain proteins have been observed in nearly a quarter of mothers of children with ASD relative to only 1% in mothers of unaffected children [26, 27••]. In humans, maternal IgG antibodies readily cross the placenta during pregnancy to equip the immunologically naïve fetus with antibodies to protect against infectious agents; these maternal IgG antibodies persist up to 6 months postnatally [127]. However, a long with IgG antibodies that are immunoprotective, autoantibodies that react to fetal ‘self’-proteins will also cross the placenta, and a number of neonatal autoimmune diseases are known to result from this transfer of pathogenic maternal IgG [128–130]. Reports of maternal IgG antibodies reactive to fetal brain proteins in mothers of children with autism suggest a possible similar role of these autoantibodies in autism [131, 132, 133••]. Others independently confirmed these findings [134], and additional studies have confirmed that these autoantibodies are present in mothers for up to 18 years following the birth of the affected child [135]. Furthermore, these ASD-specific maternal autoantibodies have been demonstrated to produce ASD-relevant behaviors in animal models [136••]. In a non-human primate study, IgG was isolated from mothers of children with autism and the autoantibodies were administered to rhesus monkeys during gestation, resulting in profound increased whole-body stereotypies and motor activity at 15 months [137], supporting a pathogenic role of these maternal autoantibodies for at least some cases of autism. A subsequent study in humans has identified the specific autoantibodies involved as reactive towards the fetal brain proteins lactate dehydrogenase A and B (LDH-A, LDH-B), collapsin

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response mediator proteins 1 and 2 (CRMP1, CRMP2), Y-box binding protein 1 (YBX1), stress-induced phosphoprotein 1 (STIP1), and guanine deaminase (GDA) [27••]. Maternal reactivity to any of these autoantigens, individually or in combination, was found to be significantly associated with an outcome of ASD in the child. When all autoantigen reactivity patterns were combined, a total of in 23% of mothers of children with ASD had one of the autoantibody patterns containing two or more of the target autoantigenic proteins relative to only 1% of control mothers. An antigen-driven endogenous mouse model of maternal autoantibody-related (MAR) ASD has recently demonstrated that prenatal exposure to these ASD-specific maternal autoantibodies resulted in ASD-relevant alterations to behavior and neuroanatomical measures in prenatally exposed male and female offspring [138••].

Immune dysregulation that suggests altered adaptive immune function is observed in individuals with ASD themselves, including neuroglial (i.e., microglial) activation and CNS inflammation [139, 140] and plasma antibodies reactive to neuronal tissue [134] in children with autism. Non-human primate studies have demonstrated that these antibody profiles in ASD may be related to early neurodevelopmental alterations, as IgG from mothers of children with ASD injected into pregnant macaques resulted in brain overgrowth in exposed offspring, specific to males [141•].

As stress affects immunity [142], and maternal immune challenges such as infection during pregnancy increase ASD risk [103], the roles of brain-reactive autoantibodies and other immune molecules are of significant interest for understanding prenatal exposure more broadly. In many settings, chronic stress is considered an immunosuppressant. However, the immunosuppressant effects of stress can cause paradoxical proinflammatory reactions by reactivation of latent viruses [143] and acute stress responses may be pro-inflammatory [144]. Prenatal stress effects on microglia in mouse offspring involve maternal IL-6 signaling [145•]. Prenatal stress has been demonstrated to increase cord blood IgE levels [146] and, in a non-human primate model, may influence maternal transfer of IgG to offspring in a sex-dependent manner [147]. Furthermore, recent evidence revealed strong relationships between SERT function, a significant player in stress regulation, and immune response, including SERT expression in B cells responsible for antibody production [148]. With these known interactions between stress, serotonin, and immunity, it will be of interest to see how these and other stress-related factors interact in clinical populations at risk for autism.

Conclusions

While genetic factors are a major contributor to the etiology of ASD, mounting evidence has supported a role for environmental factors. Some of these factors have been shown to contribute a modest increased risk for development of ASD. Prenatal stress and maternal immune dysfunction appear to contribute to a significant proportion of ASD cases. Efforts towards gaining a better understanding of how these factors interact with genetic susceptibility, particularly in mothers, will result in an increased ability to identify those individuals at greatest risk of developing ASD with such exposures. Future work is also needed to better understand the relationship between these factors and offspring sex, as

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several lines of evidence suggest greater susceptibility in male offspring in animal models, but this has not yet been consistently observed in human epidemiological studies. Furthermore, research aimed at gaining an understanding of downstream mechanisms will allow for the identification of multiple potential points for prevention or intervention. Such an intervention would be a unique opportunity for environmental-associated ASD cases. It will also be important to see if these factors result in common downstream mechanistic pathways with some of the genetic contributors to ASD, allowing for a more comprehensive approach for intervention in ASD based on personalized therapeutic approaches [149••].

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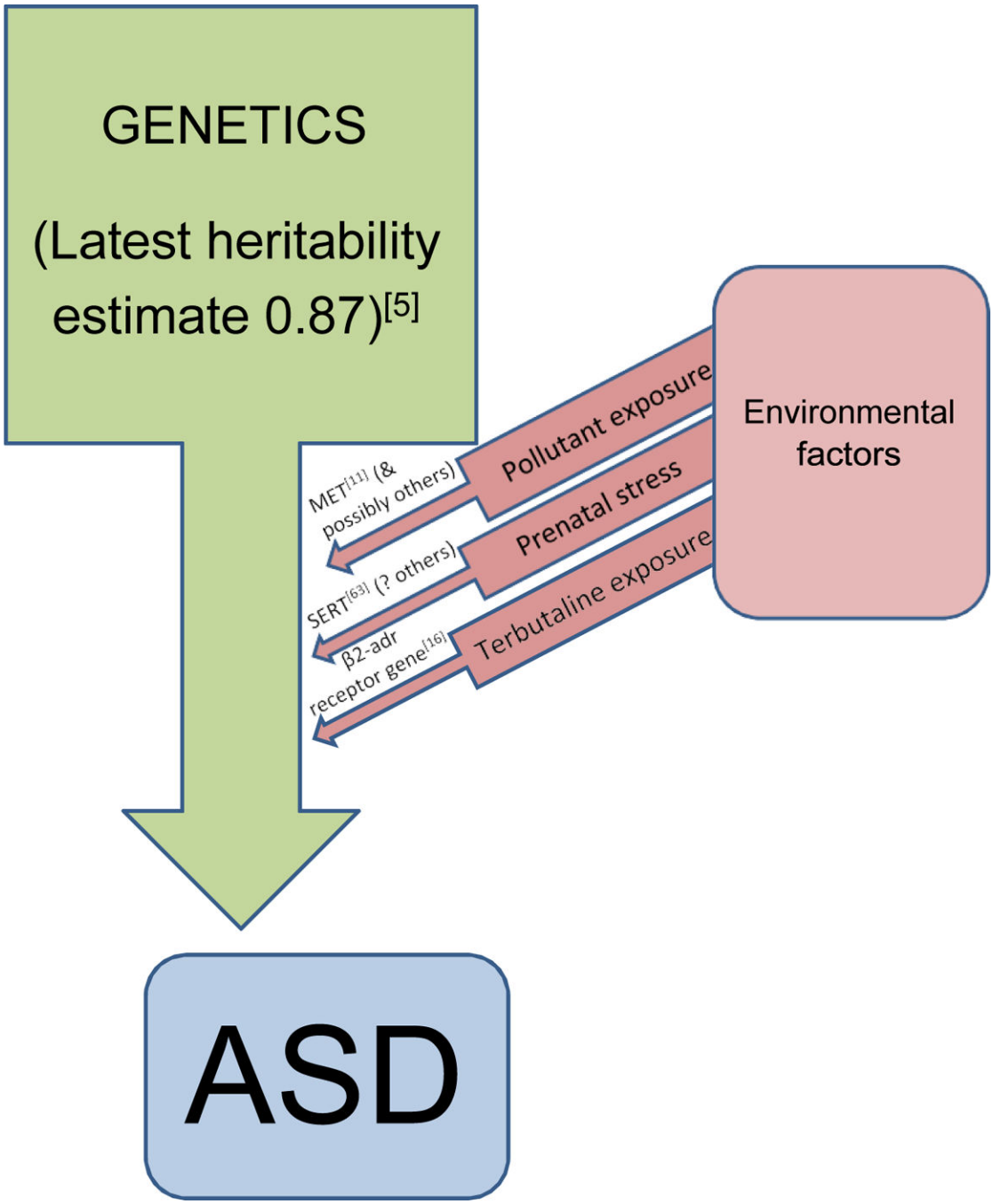

Fig. 1.

Examples of some environmental factors known to interact with genetics, augmenting the relative risk in selected cases beyond the modest relative risk of the environmental factors in isolation

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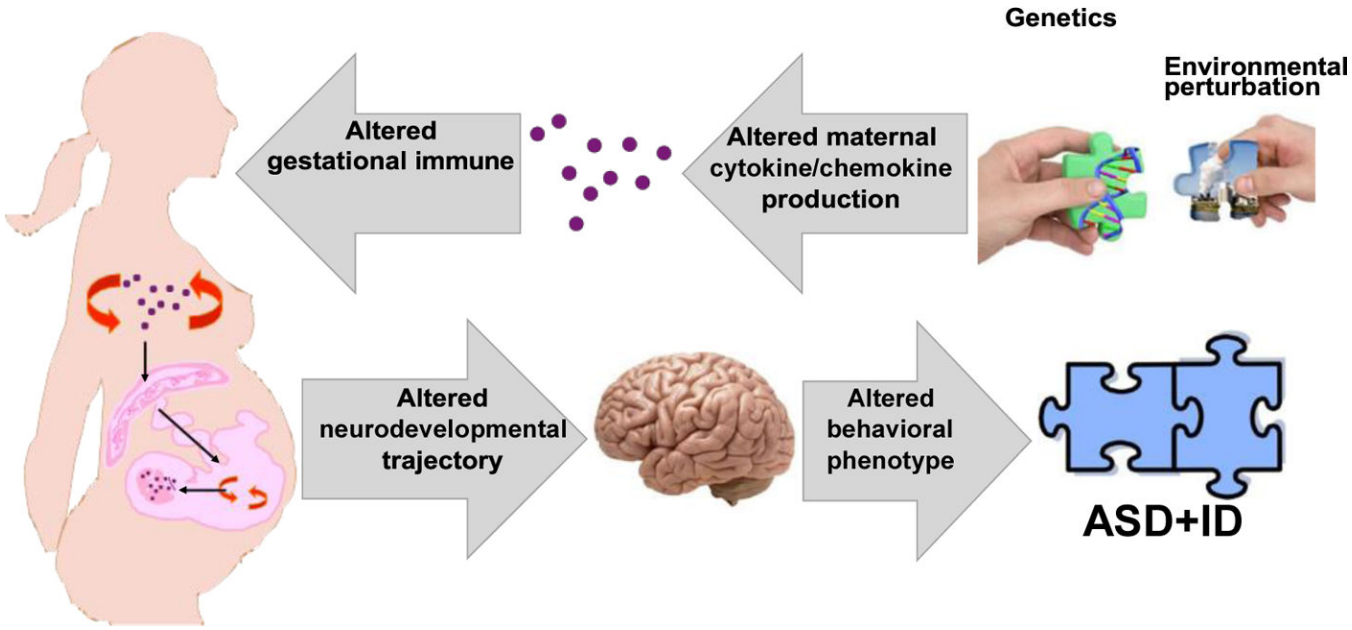

Fig. 2.

Proposed etiological pathway illustrating how elevated midgestational maternal cytokines and chemokines may lead to increased risk of ASD with intellectual disability. Genetic and environmental risk factors, either individually or in combination, can alter the production of circulating levels of inflammatory T cell and innate immune cell cytokines and chemokines in women. As these immune analytes are normally downregulated during mid-gestation, persistent elevation of these inflammatory maternal cytokines and chemokines throughout pregnancy lead to an altered gestational immune environment. This can lead to changes in the neurodevelopmental trajectory of the developing child, as there is a fine balance of immune signaling molecules needed to participate in healthy neurodevelopment. In turn, these alterations to neurodevelopment can manifest in neurodevelopmental disorders such as ASD with intellectual disability (ASD+ID)

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Table 1

Summary of reports of association between prenatal stress and clinical ASD in the literature

Study	Type	Finding
Beversdorf et al. [24]	Retrospective survey	Significantly greater incidence of prenatal stress exposure by retrospective survey specifically at 21–32 weeks gestation among 188 ASD mothers as compared to 212 control mothers
Kinney et al. [25]	Population-based cohort (Louisiana Department of Health)	Significant increased incidence of autism births in children at gestational age of 5–6 months during time of tropical storm or hurricane exposure in Orleans parish, and relationship to severity of storm
Class Li et al.[35]	Population-based-cohort(Danish Registries)	Maternal bereavement during prenatal period was not associated with increased risk of autism in the offspring when maternal psychiatric history, offspring gender and other factors were adjusted for (risk ratio 1.0), but the risk ratio was higher before adjustment (risk ratio 1.39). (2367 autism cases, 1,492,709 in study)
Class et al.[37••]	Population-based cohort(Swedish Registries)	Third trimester prenatal stress (death of first-degree relative) increased risk of ASD (adjusted risk ratio 1.58, 6430 ASD cases, 2,155,221 in study).
Roberts et al. [38••]	Population-based cohort (Nurses' Health Study II)	Significant increased risk in children of women who reported fear of abuse (sexual, emotional, physical) in the 2 years before birth year (risk ratio 2.16, 451 autism cases, 54,412 in study)
Wadler et al. [40•]	Population-based cohort (tracking 1140 mothers pregnant during Quebec ice storm)	Severe maternal depression, perinatal life stress events, male sex of child, objective hardship, subjective distress, and timing of exposure (first trimester) explained 42.7% of the variance in Autism Spectrum Screening Questionnaire scores in offspring
Hecht et al. [63••]	Retrospective survey	Significantly greater incidence of prenatal stress exposure by retrospective survey only among mothers with at least one copy of the short allele of 5-HTTLPR, observed in 2 independent samples (n=59, 99)